

NOV 1 2005

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

JANE MASSEY LICATA
LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053Docket System
Status Report
Docket Book11/8/05 ISR/WO
2/8/06 Rely WO/demand

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

08 NOV 2005

Applicant's or agent's file reference
DEX-0531

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US05/03211International filing date
(day/month/year) 03 February 2005 (03.02.2005)Applicant
DIADEXUS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Shafiqul Haq

Telephone No. (571) 272-1600

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|--|---|
| Applicant's or agent's file reference DEX-0531 | FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small> | |
| International application No. PCT/US05/03211 | International filing date (<i>day/month/year</i>) 03 February 2005 (03.02.2005) | (Earliest) Priority Date (<i>day/month/year</i>) 03 February 2004 (03.02.2004) |
| Applicant DIADEXUS, INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of:



the international application in the language in which it was filed.



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.



b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/03211

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/53, 33/573; C07K 16/00

US CL : 435/7.1, 7.4, 7.72, 7.92; 436/548; 530/387.1, 388.9, 389.8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 7.4, 7.72, 7.92; 436/548; 530/387.1, 388.9, 389.8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | KUJIRAOKA et al. Altered distribution of plasma PAF-AH between HDLs and other lipoproteins in hyperlipidemia and diabetes mellitus. Journal of Lipid Research. 2003, Vol. 44, pages 2006-2014, especially pages 2008-2010. | 1-72 |
| Y | KOSAKA et al. Spectrophotometric assay for serum platelet-activating factor acetylhydrolase activity. Clinica Chimica Acta. 2000, Vol. 296, pages 151-161, especially pages 153-154. | 1-72 |
| Y | US 2002/0177209 A1 (MACPHEE et al.) 28 November 2002, especially paras [0002-0008], [0060-0063], [0110-0114] and claims 22-24. | 73-91 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "E" earlier application or patent published on or after the international filing date | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

28 October 2005 (28.10.2005)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Date of mailing of the international search report

08 NOV 2005

Authorized officer

Shafiqul Haq

Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/03211

Continuation of B. FIELDS SEARCHED Item 3:

APS, CAPLUS

Search terms: Lp-PLA2, lipoprotein-associated phospholipase A2, PAF-AH, PAF acetylhydrolase, platlet activating factor acetylhydrolase, platlet activating factor hydrolase, detect?, analys?, determin?, measur?, ELISA, immunoassay, antib?, immobiliz?, support, substrate, inhibitor.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
JANE MASSEY LICATA
LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

Date of mailing
(day/month/year) **08 NOV 2005**

Applicant's or agent's file reference

FOR FURTHER ACTION

See paragraph 2 below

DEX-0531

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US05/03211

03 February 2005 (03.02.2005)

03 February 2004 (03.02.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 33/53, 33/573; C07K 16/00 and US Cl.: 435/7.1, 7.4, 7.72, 7.92; 436/548; 530/387.1, 388.9, 389.8

Applicant

DIADEXUS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Date of completion of this opinion
28 October 2005 (28.10.2005)

Authorized officer
Shaniqui Haq

Telephone No. (571) 272-1600

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/03211

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/03214

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-91</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive step (IS) | Claims <u>NONE</u> | YES |
| | Claims <u>1-91</u> | NO |
| Industrial applicability (IA) | Claims <u>1-91</u> | YES |
| | Claims <u>NONE</u> | NO |

2. Citations and explanations:

(1) Claims 1-72 lack an inventive step under PCT Article 33(3) as being obvious over Kujiraoka et al. (Journal of lipid research 2003) in view of Kosaka et al. (Clinica Chimica Acta 2000).

Kujiraoka et al disclose detection of PAF-AH (also known as Lp-PLA2) in a sample using immobilized monoclonal antibody on microtiter plate (see "measurement of plasma total PAF-HA concentration" in page 2008). PAF-HA that is bound to monoclonal antibody is then detected by biotinylated second antibody.

Kujiraoka et al fail to disclose using substrate of PAF-HA (as claimed in claim 8 of present invention) for spectrometric detection.

Kosaka et al., in a spectrophotometric assay for detection of PAF-AH (pages 151-155), disclose several PAF analogues containing 4-nitrophenyl groups as substrates for PAF-HA (see page 154) that read on the substrates of claims 8, 51 and 68 of present application. Kosaka et al also disclose that PAF-HA activity is related to atherosclerotic diseases.

Therefore, considering the fact that substrate for PAF-AH (Lp-PLA2) is common and known in the art (Kosaka et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to substitute biotinylated second antibody of Kujiraoka et al, with PFA-HA substrates (as disclosed by Kosaka et al.) in the method of Kujiraoka et al, with the expectation of similarly detecting/monitoring PAF-AH (Lp-PLA2) activity in a sample.

The packaging of components in kit form (claims 67-72) is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

(2) Claims 73-91 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraphs (1) and further in view of MacPhee et al. (US 2002/0177209 A1).

Kujiraoka et al. and Kosaka et al. disclose immunoassay for detection of Lp-PLA2 in a sample using monoclonal antibody against Lp-PLA2 and a substrate containing nitrophenyl group as discussed in paragraph 1 above.

However, they fail to disclose Lp-PLA2 substrate containing sulfur (S) (i.e formula (a) of present invention wherein X=S) for detection.

MacPhee et al. disclose several substrates (see formula (I) of page 1 and paragraph [0063]) and at least one of them relates to substrate of claim 80 (see for example, paragraph [0006] wherein, X=sulphur) of present application. MacPhee et al. disclose use of the substrate as a measure of enzyme activity (Lp-PLA2 activity) in a sample by immunoassay (Paragraphs [0060-0063 and 0110-0114] and claims 22-24).

Therefore, considering the fact that substrate for PAF-AH (Lp-PLA2) is common and known in the art (MacPhee et al. and Kosaka et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to substitute biotinylated second antibody of Kujiraoka et al, with PFA-HA substrates (as disclosed by MacPhee et al.) in the method of Kujiraoka et al, with the expectation of similarly detecting/monitoring PFA-AH (Lp-PLA2) activity in a sample.

The packaging of components in kit form (claims 86-91) is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

(3) Claims 1-91 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.